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Evaluation of fenitrothion for the control of malaria

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Fenitrothion was evaluated for residual spraying in antimalaria programmes in a large-scale field trial near Kisumu, Kenya from 1972 to 1976. The insecticide was applied in a hyper/holoendemic malarious area of 200 km² inhabited by about 50 000 people. All houses and animal shelters were sprayed at a target dosage rate of 2 g/m² at 3-month intervals for a total of 8 consecutive spray rounds in 2 years. The malaria vectors Anopheles gambiae *species A and B and* A. funestus *were reduced to negligible densities indoors and outdoors immediately after initiation of spraying and for 10 months after the last spray round. However,* A. gambiae *reappeared during the main wet season at densities high enough to re-establish low-level transmission for short periods. Spraying produced a marked and rapid decrease in both the incidence and prevalence of malaria. The daily probability of acquiring malaria infection was reduced from 0.009 before spraying to 0.0003 under spray protection, a reduction of 96%. Data collected on a longitudinal basis indicated that sustained spray protection would reduce malaria prevalence to an asymptotic limit of 6.9% under the assumption that the inoculation and recovery rates remain stable. However, to attain malaria eradication in this type of epidemiological situation, complementary measures such as mass drug administration appear to be necessary.*

As part of the WHO Programme for the Evaluation and Testing of New Insecticides (*1*), a field research project was carried out jointly by the World Health Organization and the Government of Kenya from 1972 to 1976 to evaluate fenitrothion as a candidate insecticide for the control of malaria. The project was located 20 km west of Kisumu town on the shores of Lake Victoria, in a rural area with a relatively stable population where there were no antimalaria measures, such as drug administration or pesticide spraying for either public health or agricultural purposes.

The climate is of the equatorial type, with an annual rainfall averaging 1335 mm during the 4-year period January 1972–December 1975. The mean temperature was 22.1°C with a maximum of 28.5°C and a minimum of 18.8°C. The climatological pattern favours perennial malaria transmission.

The malaria in this region is of the hyper/holoendemic type. *Plasmodium falciparum* is the dominant species and *P. malariae* is quite common; *P. ovale* and *P. vivax* are seldom encountered. The recognized malaria vectors, *Anopheles gambiae* (species A and B) and *A. funestus*, are both common throughout the area.

The territory selected for the trial was divided into three zones (Fig. 1): the evaluation zone (treated area) with a population of 17 000; the comparison zone (untreated area) with a population of 3800; and the barrier zone with a population of 32 000. This last zone, 3–5 km wide, was to protect the population of the evaluation zone against reintroduction of insect vectors.

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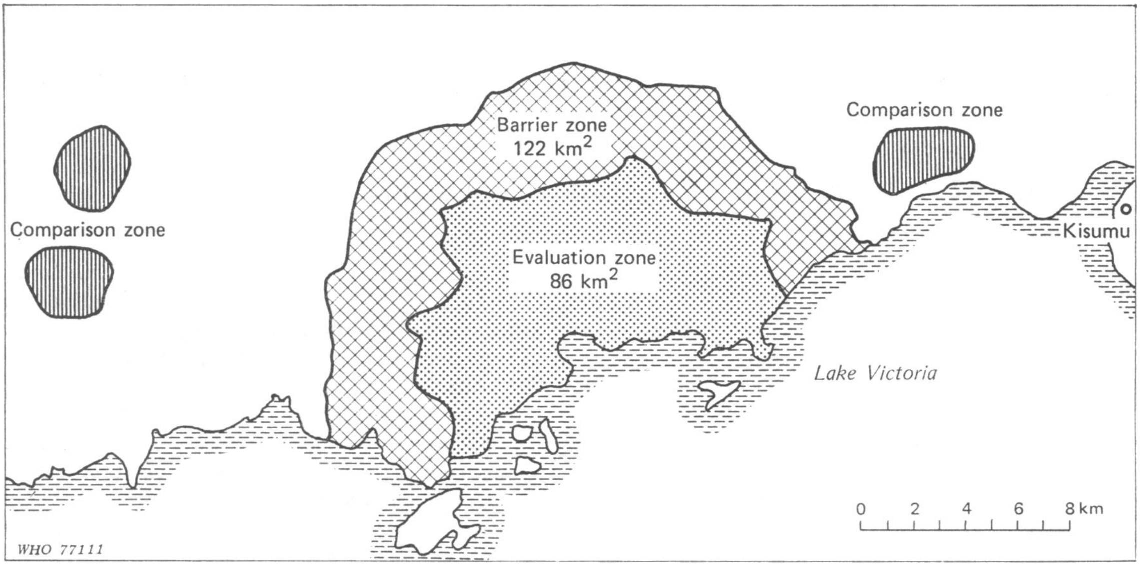

Fig. 1. The trial area in Nyanza Province, Kenya.

Fenitrothion (40% wettable powder) was applied inside dwellings at a fixed dosage of 2 g technical product/m² at intervals of 3 months. The first coverage of the treatment area was completed in August 1973 and the last in June 1975. During each of the 8 applications of the insecticide, house coverage was over 99%.

The cost factors involved in the spraying operations, based on an average of US$2100 per tonne of fenitrothion in 1975, were as follows:

	Cost (US$)	*Percentage of total*
Insecticide and local shipping (78.3 tonnes)	170 140	65.11
Salaries and wages	59 740	22.85
Transport	18 260	06.99
Spraying equipment	5 770	02.22
Field station and maintenance	5 460	02.08
Geographical reconnaissance	1 950	00.75
	261 320	100

The average cost of one spray round was $32 665 and each family compound cost nearly $6 to spray once. The *per caput* cost per round in a population of approximately 40 000 people was $0.81, or $3.24 per annum.

The activities carried out in both the evaluation and the comparison zones prior to and after the first application of fenitrothion in August 1973 were directed towards the collection of data related to:

(*a*) parasitological variables (*2*), in particular malaria transmission indices and prevalence rates and their variations, under natural conditions or under the impact of the insecticide;

(*b*) entomological variables, particularly the estimation of vector densities and infectivity and the impact of the insecticide on those variables following the application of the insecticide;

(*c*) collection of vital statistics in areas with or without insecticidal protection; and

(*d*) longitudinal observations regarding toxicity of the product and safety precautions regarding its use.

PARASITOLOGICAL VARIABLES

Malaria transmission indices

Starting in August 1972, all susceptible infants aged 0–11 months were followed up once a month until found positive (*a*) prior to August 1973, in both the evaluation and comparison zones, to quantify the level of natural transmission in an undisturbed environment and (*b*) after August 1973 and up to April 1976 in the evaluation zone to assess the degree of residual transmission and in the comparison zone to quantify the level of natural transmission.

Table 1. Observed cumulated incidence of malaria in a cohort of 1000 newborn infants, in the absence of control measures, September 1972–August 1973

Age (months)	Observed monthly parasite incidence rate (%)	No. of susceptible infants	New malaria cases in the cohort		Cumulated age-specific incidence rate (%)
			Per month	Cumulated	
0		1000			
	2.4		24	24	3.6 [b]
1		976			
	18.5		181	205	20.5
2		795			
	22.8		181	386	38.6
3		614			
	28.8		177	563	56.3
4		437			
	25.2		110	673	67.3
5		327			
	22.9		108	781	78.1
6		219			
	28.2		62	843	84.3
7		157			
	23.8		37	880	88.0
8		120			
	18.8		23	903	90.3
9		97			
	(16.7) [a]		16	919	91.9
10		81			

[a] Based on fewer than 10 observations.
[b] Adjusted for 10 days' incubation.

The positive cases found, after exclusion of the previously known positive cases, constitutes a statement of the number of new cases (or incidence) during the time stated. Blood specimens collected for microscopic examination were examined for 200 thick fields before being considered negative.

The age-specific cumulated numbers and rates of new malaria cases detected by microscopic examination in an initial cohort of 1000 newborn infants before and after fenitrothion application are shown in Tables 1 and 2, respectively.

Establishment of parasite prevalence rates

Prevalence rates were established in the general population over 1 year of age. These surveys were carried out once every 6 months in groups selected at the beginning of the trial—8 groups of 250 people in the evaluation zone and 3 groups (total 1000 people) in the comparison zone. The results of these surveys are given in Table 3.

ENTOMOLOGICAL VARIABLES [a]

Vector densities

Starting in August 1972, *A. gambiae* and *A. funestus* densities were measured using different types of collection in geographically representative locations

[a] A series of papers on the entomological aspects of the project is in preparation.

Table 2. Observed cumulated incidence of malaria in a cohort of 1000 newborn infants, October 1973–April 1976

	Area under spray coverage					Comparison area				
Age (months)	Observed monthly parasite incidence rate (%)	No. of susceptible infants	New malaria cases in the cohort: Per month	New malaria cases in the cohort: Cumulated	Cumulated age-specific incidence rate (%)	Observed monthly parasite incidence rate (%)	No. of susceptible infants	New malaria cases in the cohort: Per month	New malaria cases in the cohort: Cumulated	Cumulated age-specific incidence rate (%)
0		1000					1000			
	0.15		2	2	0.3 [a]	3.5		35	35	5.25 [a]
1		998					965			
	0.08		1	3	0.3			101	136	13.6
2		997					864			
	0.63		6	9	0.9	23.9		206	342	34.2
3		991					658			
	0.7		7	16	1.6	24.8		163	505	50.5
4		984					495			
	0.8		7	23	2.3	17.2		85	590	59.0
5		977					410			
	1.0		10	33	3.3	18.5		76	666	66.6
6		967					334			
	2.3		22	55	5.5	23.4		78	744	74.4
7		945					256			
	0.9		8	63	6.3	19.1		49	793	79.3
8		937					207			
	1.5		14	77	7.7	15.1		31	824	82.4
9		923					176			
	2.8		26	103	10.3	20.4		36	860	86.0
10		897					140			
	0.6		5	108	10.8	38.2		53	913	91.3
11		892					87			
	0.0		0	108	10.8	32.8		28	941	94.1

[a] Adjusted for an incubation period of 10 days.

in both the evaluation and the comparison zones. In particular, man–vector contact was assessed by night-biting collections.

(*a*) *Prior to the application of fenitrothion* (August 1972–July 1973). In the evaluation zone, the biting rate indoors for *A. gambiae* was 8.4 per man per night as against 6.4 for *A. funestus*. The biting rate outdoors was not assessed until June 1973 before the start of the intervention phase. The combined rate for June and July averaged 1.2 bites per man per night for *A. gambiae* and 1.6 for *A. funestus*. In the comparison zone, the biting rate indoors for *A. gambiae* was 10 per man per night as against 6.2 for *A. funestus*.

(*b*) *During the application of fenitrothion* (September 1973–May 1975). After the first application of fenitrothion, *A. gambiae* and *A. funestus* densities indoors in all collections were virtually nil. After the second application, all collections were negative despite relatively high densities in the comparison

Table 3. Parasite prevalence rates in the general population over 1 year of age before and after fenitrothion application

Date of survey	Crude prevalence rate	
	Evaluation area	Comparison area
Sept. 1972	64.5 (61.1) [a]	64.5 (59.96) [a]
March 1973	58.1 (47.6)	58.3 (50.9)
Sept. 1973	58.8 (54.2)	46.0 (41.1)
	Spraying started	
March 1974	32.1 (24.5)	56.6 (52.2)
Sept. 1974	31.4 (27.2)	55.3 (51.1)
March 1975	19.8 (16.0)	46.3 (41.7)
Sept. 1975	24.5 (21.4)	55.3 (48.1)
March 1976	17.2 (15.7)	49.0 (45.1)

[a] Figures in parentheses are the *P. falciparum* rates.

zone. The third application [a] coincided with the wet season of 1974 in March, April, and May when the monthly rainfall totalled 248, 268, and 133 mm, respectively, the highest recorded for any period during the trial. Under these conditions, *A. gambiae* reached high numbers in the comparison zone, averaging 92 per house in resting collections, whereas in the evaluation zone the density averaged only 0.14 per house. The biting rates were 0.23 per man per night in the evaluation zone and 53 in the comparison zone. Light traps produced the highest yield in the evaluation zone, averaging 1.2 per house against 166 in the comparison zone. Only two *A. funestus* females were collected. After the fourth application of the insecticide, densities were much lower in all collections owing to a combination of insecticidal effect and declining *A. gambiae* densities as confirmed by data from the comparison zone. *A. funestus* was absent in nearly all collections.

In the second year of the spray phase, involving the last four of the eight spray applications, there were no exceptional conditions encountered. Calculated dosage rates corresponded with target rates and rainfall approximated normal trends and amounts. All collections of *A. gambiae* and *A. funestus* indoors were nil or virtually nil except during the wet season of 1975. Again, *A. gambiae* reappeared as it did in the corresponding period of 1974 after the third round despite higher dosage rates, insecticidal build-up in houses from previous rounds, and a lower naturally occurring density in the comparison zone. Although the density indices in the collections were lower than the third round, the levels were sufficiently high to give rise to some transmission.

The effect of fenitrothion spraying on the outdoor vector population involved three assessment methods: outdoor resting in pit shelters and granary huts, man-biting collections, and light traps. Man-baited net traps were employed only in the final three rounds of the trial. The results of outdoor collections showed trends similar to those indoors.

The results of the spray phase clearly demonstrated a high level of effectiveness of fenitrothion residual spraying on the indoor and outdoor populations of *A. gambiae* and *A. funestus*. All indices indicated that *A. funestus* was highly amenable to control in all seasons, but *A. gambiae* reappeared during the wet season at levels sufficient to maintain transmission for a limited period despite adequate spray coverage.

(*c*) *After the intervention phase*. Results of house resting, man-biting, and light trap collections confirmed a continuing insecticidal effect 399 days after the final application of fenitrothion. All collections were negative or nearly so for *A. gambiae* in the evaluation zone until the start of the wet season in April 1976, 312–343 days after the last application. With a steep rise in natural densities in April and May, *A. gambiae* again reappeared in the evaluation zone. The resting density was 1.2 per house against 63.4 in the comparison zone and man-biting rates and light trap captures showed similar trends. In June, 379–399 days after the last spray round, natural densities in the comparison zone declined sharply but increased in the evaluation zone—a certain indication of diminishing insecticidal activity.

The results of outdoor collections showed trends similar to those indoors. The data for the two types of collection (outdoor resting and man-biting) were largely negative or nearly so until the wet season when a resurgence of *A. gambiae* occurred, reflected in a June resting density of 1.6 per granary and a biting rate of 1.1 *A. funestus* remained virtually absent in the post-spray period.

In summary, the entomology data in the post-spray period confirmed a pronounced insecticidal effect sufficient to provide a high degree of control of *A. gambiae* 371 days after spraying had ended. *A. funestus* was observed at relatively high densities in the comparison zone but was effectively suppressed in the evaluation zone. The fact that the

[a] The rate of application was less than 2 g/m².

insecticide continued to demonstrate activity 371 days after spraying, with significant suppression of house resting densities of *A. gambiae*, shows that fenitrothion could be used at longer spray cycles and/or lower dosage rates than the those employed in the trial.

Infectivity rates of the vectors

Prior to insecticide application. Dissections for the detection of sporozoites were carried out with mosquitos collected during pyrethrum spray and man-biting collections. Out of 31 488 *A. gambiae* examined, 6.56% were sporozoite positive whereas 4.3% of a total of 30 157 *A. funestus* were positive.

During the insecticide application. Out of 1010 *A. gambiae* dissected in the treated area, one was found positive for sporozoites in June 1974. In the comparison area, 4.22% out of 21 480 *A. gambiae* were found to be positive.

All 73 *A. funestus* collected in the treated area were dissected and none was found to be infected whereas 3.02% (out of 11 192 dissected) were found to be sporozoite positive in the untreated zone.

Vital statistics

Payne et al. (*3*) have studied the modification observed in general and infant mortality rates with changes in transmission induced by malaria control measures. A spectacular indirect benefit was recorded in the general mortality. The annual crude death rate decreased from 23.9 to 13.5 per 1000 population in 2 years. This indirect benefit, already noted by Bruce-Chwatt et al. (*4*) and Gramiccia et al. (*5*), deserves attention in the assessment of the impact of control measures.

The total infant death rate calculated from cohorts of 1000 newborn infants reflected, beyond doubt, the impact of vector control measures on the survival of infants since a reduction of 40.8% was observed in this rate (157 and 93 deaths per 1000 in the unprotected and protected areas, respectively).

Toxicity of fenitrothion and safety precautions

Provision was made in the spray operations for the safe storage and handling of the insecticide and the protection of spraying personnel and inhabitants of the trial area (*6*). The following measures were enforced:

(*a*) The use of protective clothing by spraymen consisting of water-repellant overalls, canvas ankle boots, broad-brimmed hats of flexible plastic, and a surgical-type face mask.

(*b*) The issue of water and soap to spraymen for removal of spray residues from exposed skin after preparation of each pump charge.

(*c*) Daily insecticide exposure limited to six hours.

(*d*) Rapid transport of spray crews after work to the field station.

(*e*) Daily showers for spraymen after work and issue of freshly laundered overalls each morning before spraying.

In addition, the blood cholinesterase activity in spraymen and other workers having frequent contact with the insecticide was monitored weekly by the tintometric method.

Although occasional operational difficulties were experienced owing to the necessity of removing spraymen with low cholinesterase activity from spraying duties, there were no clinical symptoms of toxicity observed in spraymen or in the inhabitants of the trial area or their domestic animals.

DISCUSSION

An assessment of house spraying with fenitrothion on malaria incidence, based on transmission indices, was derived from the monthly infant incidence rates shown in Tables 1 and 2.

The data assumes an initial cohort of 1000 newborn infants in the prespraying phase from which is derived the age-specific cumulated numbers and incidence rates of new malaria cases. The observed cumulated incidence corresponds to a daily parasite inoculation rate of 0.00958 for the prespraying phase (*7*).

In the spraying phase, the same data as shown for the prespraying phase is given in Table 2 for the evaluation and comparison zones covering the period October 1973 to April 1976. In this period, the daily inoculation rate in the evaluation zone was 0.00037 compared with 0.009 in the unsprayed comparison zone. Based on these rates, the effect of spraying reduced the probability of contracting malaria from once every 110 days in the comparison zone to once in 2700 days in the evaluation zone.

From a residual constant inoculation rate h of 0.00037, it is possible to estimate the malaria prevalence (L_x) in the youngest age group that could be reached if spraying of fenitrothion had continued for a longer period. According to the formula of Ross (*8*), L_x (limiting value of prevalence rate) is $h/(h+r)$ and r is the daily recovery rate of single infection,[a] which is assumed to be 0.005 for *P. falciparum*. Using the above values of h and r, L_x will reach a value of 0.069 or 6.9%.

Taking as baseline data the survey carried out in September 1973 at the time of spraying, the crude prevalence rates among the general population fell in the evaluation zone from 58.8 to 17.2 (a decrease of 70%), whereas in the untreated zone, the prevalence rates were practically left unchanged (46.0% in September 1973 as against 49.0% in March 1976).

However, residual transmission took place in the evaluation zone during the corresponding peak of transmission in the comparison zone. This is reflected by the regression line of the *P. falciparum* prevalence rate which should have fallen more steeply if the reproduction rate Z_0 had been reduced to zero. In the case of $Z_0 = 0$, *P. falciparum* prevalence should have fallen from 54.2% in September 1973 to 8.6% in September 1974—instead it was 27.2%. This was due to the remaining level of transmission. During the period October 1974–March 1976, the *P. falciparum* prevalence continued to fall to a value of 15.7% with a small recrudescence in September 1975 when it reached 21.4%.

It should be noted that prevalence and incidence were calculated for that fraction of the population which, according to fortnightly surveys, never left the treated area.

The entomological evaluation has shown fenitrothion to be a highly effective residual insecticide exerting a contact (and airborne) effect against *A. gambiae* and *A. funestus*. The vector populations were radically reduced immediately following the fiıst round of indoor spraying and were maintained at a low level throughout eight rounds of the 2-year spray phase and for 1 year beyond the final spray round when observations were discontinued. The influence of indoor spraying pervaded all facets and stages of the vector population, as shown by the disappearance of vectors for long periods from unsprayed outdoor resting shelters, by the absence of outdoor biting, and by greatly reduced larval densities in breeding habitats. The anthropophilic and endophilic preferences of the vectors enhanced the effect; this was best seen in results with the highly endophilic *A. funestus*, which was more vulnerable to control than the occasionally exophilic *A. gambiae* species A and the frequently exophilic species B.

Although control was effective, numbers of *A. gambiae* rose in the treated area during the rainy season, and house densities and man-biting densities reached levels sufficient to resume malaria transmission in the sprayed areas for about 10 weeks.

CONCLUSIONS

Indoor residual spraying with fenitrothion provided good control of malaria incidence and prevalence under conditions prevailing in the Kisumu area. The magnitude of the impact is clear from the decrease in the probability of infection from once every 110 days in the unsprayed area to once every 2700 days under spray protection, i.e., a 90% reduction in the risk of contracting malaria.

Under the holoendemic conditions existing in the trial area, continuation of residual spraying for a longer period would have reduced malaria prevalence further. However, malaria eradication would require complementary measures such as mass drug distribution during the wet period.

It is reasonable to expect that under less severe conditions varying from meso- to hyperendemicity, in East Africa or in other areas having similar transmission factors, fenitrothion residual spraying alone might stop transmission.

The findings suggest a point of diminishing returns in the capability of the insecticide applied as a residual spray to contain explosive increases in the vector population without the addition of supplementary measures, as more frequent residual spraying or higher dosage rates may not result in a higher level of control.

The high cost of the insecticide would be prohibitive for most programmes at the dosage rates and frequency of spray rounds employed in this trial. Its use in antimalaria programmes should be restricted to selective focal situations if the regimen of spraying employed in the trial were followed. Longer cycles and lower dosages might be adequately effective in certain epidemiological situations and need to be considered to reduce costs.

Toxicological data showed that the insecticide is safe to use when recommended precautions are observed.

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[a] Taking superinfection into account would lead to a slightly lower value for the actual recovery rate $R = 0.0048$ as calculated by the formula $R = h/[\exp(h/r)—1]$ quoted by Dietz et al. (*9*). In this case the corresponding limiting value will be 7.2%.

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RÉSUMÉ

ÉVALUATION DU FENITROTHION POUR LA LUTTE CONTRE LE PALUDISME

Un essai pratique à grande échelle, qui s'est déroulé entre 1972 et 1976 au Kenya, à proximité de Kisumu, a permis d'évaluer l'efficacité de pulvérisations à effet rémanent de fénitrothion dans des programmes antipaludiques. L'insecticide a été appliqué dans une zone impaludée hyper- ou holoendémique de 200 km² où vivent quelque 50 000 ruraux. Les pulvérisations ont été effectuées sur 2 ans à raison de 2 g/m² dans toutes les habitations et abris pour animaux lors de 8 tournées séparées par un intervalle de trois mois. On a enregistré immédiatement après le début des opérations la réduction jusqu'à des densités négligeables des populations de vecteurs du paludisme *Anopheles gambiae*, espèces A et B, et *Anopheles funestus*, à l'intérieur aussi bien qu'à l'extérieur des habitations; ces effets ont persisté pendant dix mois après la dernière application d'insecticide. Les densités de *A. gambiae* constatées lors de sa réapparition au cours de la principale saison de pluies ont toutefois été assez élevées pour déclencher la reprise d'une transmission de faible intensité pendant de courtes périodes. Les pulvérisations ont eu pour effet une diminution prononcée et rapide de l'incidence et de la prévalence du paludisme. Le taux journalier d'inoculation a été réduit pour la population protégée à 0,00037 contre 0,009 avant les pulvérisations, ce qui représente une diminution de 96% de la probabilité journalière de contracter l'infection paludique. On estime, sur la base d'une enquête longitudinale, qu'une protection permanente de ce type réduirait la prévalence du paludisme à la valeur limite de 6,9%, en supposant que les taux résiduels d'inoculation et de guérison journalières demeurent constants.